REMARKS

Applicant has cancelled claims 1-3 without prejudice, expressly reserving the right to pursue the subject matter of the cancelled claims in one or more subsequent applications.

Applicant has amended claims 15, 17 and 19 to delete the text relating to "cells capable of producing an angiogenic factor." Applicant has also amended claims 15, 17 and 19 to recite that the amount of the angiogenic factor is "... an amount sufficient to stimulate collateral blood vessel formation in said ischemic or diseased heart" (claim 15); "...an amount sufficient to induce angiogenesis in said ischemic or diseased heart" (claim 17), and; "...an amount sufficient to improve contractile function of said ischemic or diseased heart. Applicant has also amended claim 21 to recite that the therapeutic agent is delivered to the myocardium of the ischemic or diseased heart in an amount sufficient to stimulate tissue regeneration in said ischemic or diseased heart. Applicant has amended claim 38 to recite that the therapeutic agent is delivered to normal myocardial tissue "in an ischemic or diseased heart" in an amount sufficient to ameliorate the symptoms of ischemia. Support for these amendments if found in the specification on page 6, lines 5-10.

Applicants have amended claim 52 such that it does not refer to withdrawn claims.

Applicant has developed a method that produces surprising results: greater levels of collateral blood vessel formation and angiogenesis are induced in ischemic or diseased hearts when the therapeutic agent is injected into the normal tissue of the diseased heart as opposed to injecting the agent into the ischemic tissue in the diseased heart. This is a completely unexpected result. The prior art, including Kornowski *et al.*, Catheterization and Cardiovascular Interventions 48:447-453, 1999 cited by the Examiner, does not teach or suggest injecting a therapeutic agent into the normal tissue of a diseased heart to achieve the superior therapeutic effect disclosed by Applicants.

35 U.S.C. 112, SECOND PARAGRAPH – INDEFINITENESS

Claims 15, 17 and 19 are objected to under 35 U.S.C. §112, second paragraph for purportedly being indefinite. In particular the Examiner contends that the claims contain non-elected subject matter. Applicant has amended claims 15, 17 and 19 such that they do not refer to injection of "cells capable of producing an angiogenic factor."

In view of the amendment of the claims applicants request that the Examiner reconsider and withdraw the objection of the claims.

35 U.S.C. § 112, FIRST PARAGRAPH - WRITTEN DESCRIPTION

Claims 1-3, 15, 17, 19, 21, 36-40 and 52-54 stand rejected under 35 U.S.C. § 112, first paragraph for purportedly failing to comply with the written description requirement. In particular, the Examiner contends that when the claimed invention is interpreted in light of the specification it encompasses any cell or cells, any one or more drugs, an antisense DNA or RNA or any other therapeutic agent useful to induce angiogenesis, increase contractile function in the heart, increase blood flow within the heart, stimulate collateral vessel development in the heart, promote tissue regeneration, improve exercise tolerance, or treat myocardial ischemia. The Examiner contends that the specification does not describe any of these agents. Applicant respectfully disagrees and in view of the amendments to the claims and the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection of the claims.

Applicant has cancelled claims 1-3 without prejudice and therefore addresses the rejection as it pertains to the remaining claims. Claims 15, 17 and 19 relate to methods for stimulating collateral blood vessel formation in the myocardium (claim 15), inducing angiogenesis in the myocardium (claim 17) or improving contractile function of a diseased heart (claim 19), by delivering an angiogenic factor to normal tissue in an ischemic or diseased heart. The specification provides numerous specific examples of angiogenic factors, e.g., fibroblast growth factors, endothelial cell growth factors or other proteins with such biological activity (see page 8, line 27 to page 9, line 16). In particular see page 9, lines 2-6 which recite, e.g., FGF-1, FGF-2, FGF-5, VEGF and active fragments thereof such as $VEGF_{165}$, as well as HIF-1, PDGF-1, PDGF-2, DEL1, angioprotein, HGF, MCP-1, eNOS and iNOS. The specification recites other proteins that are also useful in this invention, e.g. factors involved in myocardial preservation or

reperfusion injury, such as heme oxygenase, hKis, AKT, PR39 and βarkCT (page 9, lines 13-14). Applicant has disclosed amounts of the factors that would be effective in the methods of this invention (see page 11, line 27 to page 12, line 7). Applicant has directed those of skill in the art to deliver the therapeutic agent intramyocardially to normal tissue in an ischemic heart in amounts effective to promote tissue regeneration (page 3, lines 16-21). Applicant's Examples demonstrate the stimulation of collateral blood vessel formation in the myocardium, the induction of angiogenesis in the myocardium and the improvement in the contractile function of a ischemic heart by delivering 10 injections of 20ul each of $5x10^9$pfu/ml Ad-$VEGF_{165}$, to the normal tissue of an ischemic heart.

Claims 21-37 relate to a method for promoting tissue regeneration in an ischemic or diseased heart by delivering a therapeutic agent to normal tissue in the heart (claim 21), particularly a protein, nucleic acid molecule, or drug which promotes regeneration (claim 36), more particularly CD34 ligand or the c-kit ligand (claim 37). Applicant's specification discloses numerous specific examples of therapeutic agents that may be delivered to the normal tissue of an ischemic or diseased heart. Applicant has disclosed that the recited therapeutic agents are useful for inducing angiogenesis, increasing contractile function in the heart, increasing blood flow within the heart, stimulating collateral vessel development in the heart, and promoting tissue regeneration. Applicants disclose that suitable therapeutic agents for use in this invention include gene therapy vectors, angiogenic proteins or peptides (as discussed supra), transgenes encoding the angiogenic proteins or peptides, a cell or cells which express a therapeutic agent, whole bone marrow, one or more drugs, and antisense RNA or DNA (page 6, lines 22-23). The suitable gene therapy vector may be replication deficient adenovirus, a recombinant adeno-associated virus vector (rAAV), a retroviral vector or a plasmid (page 6, lies 27-29). The specification recites specific factors involved in tissue regeneration, e.g., ligands for progenitor or stem cells, e.g., c-kit and CD34 ligand (page 9, lines 14-16). As discussed *supra*, Applicant has directed those of skill in the art to deliver the therapeutic agent intramyocardially to normal tissue in an ischemic heart in amounts effective to promote tissue regeneration (page 3, lines 16-21).

Claims 38-53 relate to a method for treating myocardial ischemia which comprises delivering a therapeutic agent to normal myocardial tissue to ameliorate the symptoms of

ischemia. Applicants disclose that suitable therapeutic agents for use in this invention include gene therapy vectors, angiogenic proteins or peptides (as discussed supra), transgenes encoding the angiogenic proteins or peptides, a cell or cells which express a therapeutic agent, whole bone marrow, one or more drugs, and antisense RNA or DNA (page 6, lines 22-23). The suitable gene therapy vector may be replication deficient adenovirus, a recombinant adeno-associated virus vector (rAAV), a retroviral vector or a plasmid (page 6, lies 27-29). The vector may include a transgene encoding a protein or angiogenic factor described in the specification, e.g., factors involved in myocardial preservation or reperfusion injury, and tissue regeneration, such as e.g., heme oxygenase, hkis, AKT, PR39, βarkCT , C-kit ligand and CD34. Applicant has instructed those of skill in the art to deliver the therapeutic agent to normal myocardial tissue in an ischemic heart and Applicant has disclosed that the amelioration of symptoms associated with myocardial ischemia includes, increased tolerance to exercise, decreased chest pain and decreased shortness of breath.

Furthermore, the specification teaches intramyocardially delivering a therapeutic agent specifically to the normal tissue of an ischemic or diseased heart. Particularly, the specification exemplifies the intramyocardial delivery of an Ad-$VEGF_{165}$ vector in a therapeutically effective amount to normal and ischemic tissue of an ischemic heart using the method as claimed. The specification exemplifies the stimulation of collateral blood vessel formation in an ischemic heart (see Example 1 and Figure 9), the induction of angiogenesis (see Example 1 and Figure 9), and an improvement in contractile function (see Example 2 and Figure 7).

Regarding the delivery of the therapeutic agent to the heart, the specification teaches the intramyocardial delivery of the therapeutic agent specifically to the normal tissue of the ischemic or diseased heart. Thus the method would be applicable to any therapeutic agent for delivery to the normal tissue of the ischemic heart. Applicant has explicitly described a variety of delivery methods e.g. infusion catheter, diagnostic catheter, stiletto catheter, needle or needles, needle-free injector, balloon catheter, or channeling device useful for intramyocardially delivering a therapeutic agent specifically to normal tissue in a diseased or ischemic heart. Applicant has exemplified the delivery of an Ad-$VEGF_{165}$ vector to the normal tissue of an ischemic heart using an injection catheter. The exemplified delivery of VEGF to the normal tissue of the heart by intramyocardial delivery with an injection catheter is representative of the genus for delivery.

One of skill in the art would recognize that Applicants were in possession of all of the various delivery methods necessary to practice the claimed invention.

The claims also recite that the therapeutic agent is delivered in a therapeutically effective amount. Applicant directs the Examiner's attention to specification page 11, line 27 to page 12, line 7 wherein Applicant describes the amounts of the therapeutic agents injected into the animal that would be therapeutically effective. For example, Applicant teaches that for an agent such as a gene therapy vector, e.g., a replication defective adenovirus, the dosage can range from about 10^6 to about 10^{12} plaque-forming units (pfu) and is preferably between about 10^8 to about 10^{10} pfu. Applicant also teaches the range suitable for another agent e.g., rAAV, of about 1 x 10^5 IU (infectious units) of rAAV per gram body weight to about 1 x 10^9 IU AAV per gram body weight, preferably 1 x 10^6 to 1x 10^7 IU AAV per gram body weight. Applicant also teaches the therapeutically effective dosage for a therapeutic agent that is a protein, e.g., from as little as 1 picogram to several hundred micrograms. The description of the dosage amounts of various therapeutic agents provides sufficient description for one of skill in the art to recognize that Applicant was in possession of the agent's "therapeutically effective amount" as recited in the claims.

The foregoing demonstrates that the specification provides numerous examples of members of the genus "therapeutic agents" and the genus "angiogenic factors". and factors involved in "tissue regeneration" that would be useful in the claimed method, e.g., gene therapy vectors, angiogenic proteins or peptides (as discussed supra), transgenes encoding the angiogenic proteins or peptides, a cell or cells which express a therapeutic agent, whole bone marrow, one or more drugs, and antisense RNA or DNA (page 6, lines 22-23) and particularly, proteins an vectors comprising transgenes encoding proteins such as, FGF-1, FGF-2, FGF-5, VEGF and active fragments thereof such as $VEGF_{165}$, as well as HIF-1, PDGF-1, PDGF-2, DEL1, angioprotein, HGF, MCP-1, eNOS and iNOS, heme oxygenase, hKis, AKT, PR39 and βarkCT (page 9, lines 13-14). The foregoing also demonstrates that applicant disclosed that the agents and factors should be delivered to the normal tissue of a diseased or ischemic heart, disclosed various method for delivery to the normal tissue and also disclosed amounts that would be effective in the claimed methods. As such Applicant's disclosure reasonably conveys to one of skill in the art that the inventor had possession of the claimed subject matter at the time of filing,

thus satisfying the written description requirement of 35 U.S.C. 112, first paragraph. The written description requirement does not require a recitation of all the members of a genus, just so many as to reasonably convey to one of skill in the art that Applicant was in possession of the invention at the time of filing.

In view of the foregoing remarks Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 112, first paragraph for purportedly lacking written description.

35 U.S.C. 112, FIRST PARAGRAPH - ENABLEMENT

Claims 1-3, 15, 17, 19, 21, 36-40 and 52-54 stand rejected under 35 U.S.C. 112, first paragraph for purportedly being non-enabled. In particular, the Examiner contends that the specification does not provide any guidance as to how all the agents would have been delivered to the recited sites in an animal to treat any condition in the heart. Applicant respectfully disagrees.

> "A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation. It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification."
>
> *Northern Telecom, In. v. Datapoint Corp.*, 15 USPQ 1321, 1329 (Fed. Cir.1990)

Applicant cancelled claims 1-3 without prejudice and as such Applicant addresses the foregoing rejection as it pertains to the remaining claims. Applicant has taught that the therapeutic agent is myocardially delivered to the normal tissue of an ischemic or diseased heart. Particularly the therapeutic agent may be delivered to normal tissue that is adjacent to a zone of ischemic myocardium, or ischemic myocardial tissue, or the therapeutic agent may be injected into multiple sites distributed throughout the normal myocardium of the diseased heart (see, e.g., page 5, lines 24-26). Applicant has also disclosed various myocardial delivery methods, e.g., stiletto catheter, needle or needles, needle-free injector, balloon catheter, or channeling device (see e.g., page 12, lines 19-20). Thus one of skill in the art could intramyocardially deliver any therapeutic agent specifically to normal tissue in the ischemic heart adjacent to the ischemic

tissue or throughout the normal myocardium without undue experimentation.

Moreover, applicant has disclosed particular proteins, e.g., angiogenic factors and factors that promote tissue regeneration that are useful in the methods of this invention, e.g., FGF-1, FGF-2, FGF-5, VEGF and active fragments thereof such as $VEGF_{165}$, as well as HIF-1, PDGF-1, PDGF-2, DEL1, angioprotein, HGF, MCP-1, eNOS and iNOS, (page 9, lines 2-6) heme oxygenase, hKis, AKT, PR39 and βarkCT (page 9, lines 13-14).

The Examiner contends that the specification fails to provide any guidance as to what doses of any agent will be delivered which would provide a therapeutic effect. Applicant again directs the Examiner's attention to specification page 11, line 27 to page 12, line 7 wherein Applicant describes various amounts of therapeutic agents injected into the animal that would be therapeutically effective. For example, Applicant teaches that an agent such as a gene therapy vector e.g., a replication defective adenovirus, the dosage can range from about 10^6 to about 10^{12} plaque-forming units (pfu) and is preferably between about 10^8 to about 10^{10} pfu. Applicant's Example 1 discloses 10 injections, each 20ul of 5 x 10^9pfu/ml of AD-$VEGF_{165}$. Applicant also teaches the range suitable for another agent e.g., rAAV, of about 1 x 10^5 IU (infectious units) of AAV per gram body weight to about 1 x 10^9 IU AAV per gram body weight, preferably 1 x 10^6 to 1x 10^7 IU AAV per gram body weight. Applicant also teaches the dosage for a protein agent wherein the dosage is from as little as 1 picogram to several hundred micrograms. Those of skill in the art provided with such instruction would readily and without undue experimentation determine a therapeutically effective dose of any therapeutic agent known to be useful in the treatment of heart disease, and deliver that dose specifically to the normal myocardial tissue of the ischemic or diseased heart. Those of skill in the art would readily recognize the therapeutic effect of the agent on the ischemic heart. See e.g. page 12, lines 8-17, wherein Applicants disclose that methods useful for assessing for cardiac function are well known in the art and direct those of skill in the art to those methods. A person skilled in the art, using the knowledge available to such a person and the disclosure in this application, could make and use the claimed method without undue experimentation. "It is not fatal if some experimentation is needed, for the patent document is not intended to be a production specification." *Northern Telecom, In. v. Datapoint Corp.*, 15 USPQ 1321, 1329 (Fed Cir. 1990).

THE ANTICIPATION/OBVIOUS REJECTIONS

Claims 1-3, 15, 17, 19, 21, 36-40 and 52-54 stand rejected under 35 U.S.C. § 102(b) or alternatively under 35 U.S.C. §103(a) for purportedly being anticipated by, or rendered obvious by, Kornowski *et al.*, Catheterization and Cardiovascular Interventions 48:447-453, 1999. Applicant respectfully disagrees.

> "Anticipation under 35 U.S.C. § 102 requires the disclosure in a single piece of prior art of each and every limitation of a claimed invention."
>
> *Electro Med. Sys. S.A. v. Cooper Life Sciences,* 32 USPQ2d 1017, 1019 (Fed.Cir. 1994).

The Examiner states "The art teaches drug delivery by catheter based transendocardial injection to heart" (Office Action, page 6) but simply summarizes in the most general of terms, what is disclosed in Kornowski et al. The Examiner contends that:

> on page 448 the art assessed its procedural safety and performance characteristics;
>
> on page 448-452, the Materials and Method section teaches the methodology, the instruments and the protocol in detail;
>
> page 449-541 discuss the results and characterization of the model, and;
>
> page 452-453 discuss the clinical implications of the method.

However, the Examiner has failed to point to a single instance in all the cited sections wherein Kornowski teaches one of skill in the art to inject a therapeutic agent specifically into the normal tissue of an ischemic or diseased heart. In fact, Kornowski states:

> "The objectives of this study were to evaluate the safety and certain aspects of the performance characteristics of the Biosense injection catheter system when used to inject a fluid into normal porcine hearts."
>
> (p. 452 first sentence of Discussion, emphasis added)

and,

> "It should be emphasized, however, that our experiment has no obvious clinical implication for therapeutic myocardial angiogenesis since no angiogenic relevant gene has been used in this feasibility study."
>
> (p. 453, left col., last sentence of first full paragraph)

Kornowski teaches injection of a methylene blue into normal tissue in a normal heart. Kornowski does not describe any methods wherein a therapeutic agent is injected specifically into normal tissue of a diseased or ischemic heart. Therefore, Kornowski does not teach each and every limitation of the claims, which is a requisite for a proper rejection under 35 U.S.C. § 102.

Kornowski also fails to render the invention as claimed obvious.

> "[A] proper analysis under § 103 requires, *inter alia,* consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. . . .Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the Applicant's disclosure."
>
> *In re Vaeck*, 20 USPQ2d 1438, 1442 (CAFC 1991)

Kornowski et al. does not teach or suggest delivering a therapeutic agent to the normal tissue of an ischemic or diseased heart and without such a teaching or suggestion, one of skill in the art would not have been motivated to deliver any therapeutic agent to the normal tissue of an ischemic or diseased heart, as taught by Applicant's claims. Furthermore, one of skill in the art with Kornowski in hand would not have been able to predict that injection of the therapeutic agent into the normal tissue of an ischemic or diseased heart, as opposed to injection into the ischemic tissue of the diseased heart, produced superior results.

Kornowski also fails to teach or suggest the method as described in claims 15, 17, 19, 21, 36-40 and 52-54, i.e.:

> a method to stimulate collateral blood vessel formation (claim 15), or to induce angiogenesis (claim 17), in the myocardium by intramyocardially delivering an angiogenic factor to normal tissue in an ischemic heart in an amount sufficient to stimulate collateral blood vessel formation, or induce angiogenesis;
>
> a method to improve contractile function of an ischemic heart by intramyocardially delivering an angiogenic factor to normal tissue in an

ischemic heart in an amount sufficient to improve contractile function of the heart (claim 19), or;

a method to promote tissue regeneration (claims 21, 36-40 and 52-54) by delivering a therapeutic agent to normal tissue in an ischemic or diseased heart.

Applicant teaches those of skill in the art to deliver a therapeutic agent specifically to the normal tissue of an ischemic or diseased heart. Applicant has discovered that delivering a therapeutic agent specifically into the normal tissue of a diseased or ischemic heart in a therapeutically effective amount provides a significantly better therapeutic effect than the effect of the agent when the agent is injected into the ischemic tissue of the diseased heart.

Example 1 and Figures 7 and 9 demonstrate that collateral blood vessel formation, angiogenesis and contractile function are significantly greater in ischemic hearts wherein the therapeutic agent was injected into the normal tissue as compared to ischemic hearts wherein the therapeutic agent was injected into the ischemic tissue.

In summary, there is no teaching or suggestion in Kornowski, and one of skill in the art would not have been motivated by Kornowski, to deliver the therapeutic agent to the normal tissue of a diseased or ischemic heart as opposed to delivering the agent to the ischemic or diseased tissue of the heart. And, one of skill in the art would not have expected in view of Kornowski that delivering the therapeutic agent to the normal tissue as opposed to the ischemic tissue would provide significantly better results. Thus, Kornowski fails to provide the necessary teaching or suggestion sufficient to allow those of ordinary skill in the art to carry out the claimed process; and Kornowski fails to reveal that in carrying out the claimed process, those of ordinary skill would have a reasonable expectation of producing a significantly better effect. As such, Kornowski does not render obvious Applicant's methods as claimed.

In view of the foregoing remarks and amendments to the claims applicants respectfully request that the examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. §§ 102(a) and 103(b) for purported anticipation or obviousness.

Applicants believe no fee or request for extension of time are due with this filing. However, if such a fee is due or a request for an extension of time is required applicants

authorize the Commissioner to deduct any missing or insufficient fee from Deposit Account No. 06-2375, under Order No. BSX 236 US2 10409073 and applicants request that any necessary extensions of time be granted.

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Respectfully submitted,

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